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*Admitted only in Maryland
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June 14, 2004

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Art Unit 1614

Re: U.S. Utility Patent Application
Application No. 10/721,338; Filed: November 26, 2003
For: **Caspase Inhibitors and the Use Thereof**
Inventors: Cai *et al.*
Our Ref: 1735.0350004/RWE/RAS

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Information Disclosure Statement Under 37 C.F.R. § 1.197(b);
2. Twenty-six (26) pages of Form PTO-1449 citing one hundred thirty-nine (139) references;
3. A copy of five (5) cited references; and
4. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents
June 14, 2004
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert A. Schwartzman, Ph.D.
Agent for Applicants
Registration No. 50,211

RAS/law
Enclosures
272716.1



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Cai et al.

Appl. No. 10/721,338

Filed: November 26, 2003

For: **Caspase Inhibitors and the Use
Thereof**

Art Unit: 1614

Examiner: *To Be Assigned*

Atty. Docket: 1735.0350004/RWE/RAS

Information Disclosure Statement Under 37 C.F.R. § 1.97(b)

Commissioner for Patents
Washington, D.C. 20231

Sir:

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application. Copies of documents AA1-AE3, AL1-AO6, AR1-AS6, AR7-AS20, AR21-AT22, and AS23-AR26 were cited by or submitted to the Office in an Information Disclosure Statement that complies with 37 C.F.R. § 1.98(a)-(c) in Application No. 09/987,417 filed November 14, 2001, which is relied upon for an earlier filing date under 35 U.S.C. § 120. Thus, copies of these documents are not attached. 37 C.F.R. § 1.98(d). Copies of documents AT6, AT20, AR23, AS26, and AT26 are provided.

In accordance with 37 C.F.R. § 1.98(a)(3), Applicants' undersigned representative submits the following concise explanation of the relevance of the non-English language documents, Document Nos. AM3, AO3, AT8 and AT10 cited on Form PTO-1449.

The relevance of document AM3, Japanese Application No. JP 11-1491, published January 6, 1999, can be ascertained by reference to the International Search

Report for International Application No. PCT/US00/09319 (Document AR25). An English language abstract of Document AM3 is provided as Document AS25.

Document AO3, Japanese Patent 11-180891, is in the Japanese language. An unverified English language abstract of document AO3 is provided as document AT25.

Document AT8, Hiraoka, J., *et al.*, *Jpn. J. Nephrol.* 40:276-283 (May 1998), is believed to describe a study which indicates that apoptotic cells are increased in renal amyloidosis and that overexpression of BAX, an inducer of apoptosis, may play an important role in this increase. An English language abstract of this document is provided on page 276.

Document AT10, the Ph.D. Thesis of Johann Lepschy, is believed to disclose a modified Dakin-West procedure for the synthesis of α -benzamidoalkyl trifluoromethyl ketone, including 1,1,1-trifluoro-3-benzamido-2-butanone.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist. The Examiner is specifically requested not to rely solely on the material submitted herewith. It is further understood that the Examiner will consider information that had been cited or submitted to the U.S. Patent and Trademark Office in a prior application relied on under 35 U.S.C. § 120. 1138 OG 37, 38 (May 19, 1992).

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449, and to indicate in the official file wrapper of this patent application that the documents have been considered.

This Information Disclosure Statement is being filed before the mailing of an Office Action on the merits. No statement or fee is required.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Robert A. Schwartzman, Ph.D.
Agent for Applicants
Registration No. 50,211

Date: June 14, 2004

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FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT

ATTY. DOCKET NO.
1735.0350004/RWE/BLS

APPLICATION NO.
10/721,338

APPLICANTS
Cai et al.

FILING DATE
November 26, 2003

GROUP
To Be Assigned

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB- CLASS	FILING DATE
	AA1	4,153,688	05/08/1979	Domicoli et al.			02/09/1978
	AB1	4,518,528	05/21/1985	Rasnick, D.W.			02/06/1984
	AC1	5,252,463	10/12/1993	Nelson et al.			06/22/1990
	AD1	5,416,013	05/16/1995	Black et al.			02/28/1994
	AE1	5,430,128	07/04/1995	Chapman et al.			11/21/1994
	AF1	5,434,248	07/18/1995	Chapman et al.			06/02/1993
	AG1	5,462,939	10/31/1995	Dolle et al.			05/07/1993
	AH1	5,585,357	12/17/1996	Dolle et al.			01/29/1996
	AI1	5,624,672	04/29/1997	Bathurst et al.			06/05/1995
	AJ1	5,635,186	06/03/1997	Bathurst et al.			05/30/1995
	AK1	5,635,187	06/03/1997	Bathurst et al.			06/06/1995

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL1	EP 0 519 748 A2	12/23/1992	Europe			Yes No
	AM1	WO 93/05071	03/18/1993	WIPO			Yes No
	AN1	EP 0 623 592 A1	09/11/1994	Europe			Yes No
	AO1	EP 0 618 223 A2	10/05/1994	Europe			Yes No
	AP1	WO 96/03982	02/15/1996	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>1</u>	Alnemri, E.S. et al., "Human ICE/CED-3 Protease Nomenclature," Cell 87:171, Cell Press (1996).
	AS	<u>1</u>	An, S. and Knox, K.A., "Ligation of CD40 rescues Ramos-Burkitt lymphoma B cells from calcium ionophore- and antigen receptor-triggered apoptosis by inhibiting activation of the cysteine protease CPP32/Yama and cleavage of its substrate PARP," FEBS Lett. 386:115-122, Federation of European Biochemical Societies (1996).
	AT	<u>1</u>	Angliker, H. et al., "The synthesis of lysylfluoromethanes and their properties as inhibitors of trypsin, plasmin and cathepsin B," Biochem J. 241:871-875, London Portland Press On Behalf Of The Biochemical Society (1987).

EXAMINER

DATE CONSIDERED

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FORM PTO-1449 <u>INFORMATION DISCLOSURE STATEMENT</u>	ATTY. DOCKET NO. 1735.0350004/RWE/BLS	APPLICATION NO. 10/721,338
	APPLICANTS Cai et al.	
	FILING DATE November 26, 2003	GROUP To Be Assigned

U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA2	5,677,283	10/14/1997	Dolle et al.			10/16/1996
	AB2	5,756,465	05/26/1998	Sleath et al.			05/12/1995
	AC2	5,843,904	12/01/1998	Bemis et al.			12/20/1995
	AD2	5,866,545	02/02/1999	Hagmann et al.			08/08/1994
	AE2	5,869,519	02/09/1999	Karnewsky et al.			12/16/1996
	AF2	5,871,724	02/16/1999	Iwata et al.			06/07/1995
	AG2	5,877,197	03/02/1999	Karnewsky et al.			09/12/1997
	AH2	5,932,549	08/03/1999	Allen et al.			04/27/1998
	AI2	6,136,787	10/24/2000	Black et al.			03/16/1998
	AJ2	6,153,591	11/28/2000	Cai et al.			03/16/1999
	AK2	6,184,210	02/06/2001	Keana et al.			03/16/1999

FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL2	WO 96/20721	07/11/1996	WIPO			Yes No
	AM2	WO 96/33209 A1	10/24/1996	WIPO			Yes No
	AN2	WO 98/10778	03/19/1998	WIPO			Yes No
	AO2	WO 98/11109	03/19/1998	WIPO			Yes No
	AP2	WO 98/41232	09/24/1998	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	2	Black, R.A. et al., A Pre-aspartate-specific Protease from Human Leukocytes That Cleaves Pro-interleukin-1 β , " J. Biol. Chem. 264:5323-5326, The American Society for Biochemistry and Molecular Biology, Inc. (1989).
	AS	2	Black, S.C. et al., "Co-localization of the Cysteine Protease Caspase-3 with Apoptotic Myocytes after In Vivo Myocardial Ischemia and Reperfusion in the Rat," J. Mol. Cell. Cardiol. 30:733-742, Academic Press Limited (April 1998).
	AT	2	Bourne, E.J. et al., "Studies of Trifluoroacetic Acid. Part XVIII. Reaction of N-Aroylglycines with Perfluoro-carboxylic Anhydrides." J. Chem. Soc. Part II:1771-1775, The Chemical Society (1961).

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	AA3	6,184,244 B1	02/06/2001	Karanewsky et al.			06/30/1999
	AB3	6,200,969 B1	03/13/2001	Fritz et al.			09/12/1997
	AC3	6,201,118 B1	03/13/2001	Robidoux et al.			08/19/1998
	AD3	6,242,422	06/05/2001	Karanewsky et al.			10/22/1998
	AE3	6,355,618	03/12/2002	Cai et al.			04/07/2000
	AF3	6,716,818 B2	04/06/2004	Cai et al.			11/14/2001
	AG3	6,495,522 B1	12/17/2002	Wang et al.			08/28/2000
	AH3	6,566,338 B1	05/20/2003	Weber et al.			10/11/2000
	AI3	6,596,693 B1	07/22/2003	Keana et al.			08/31/2000
	AJ3	6,620,782 B1	09/16/2003	Cai et al.			03/16/2000
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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL3	WO 98/16502 A1	04/23/1998	WIPO			Yes No
	AM3	JP 11-1491	01/06/1999	Japan			Yes X No
	AN3	WO 99/18781	04/22/1999	WIPO			Yes No
	AO3	JP 11-180891	07/06/1999	Japan			Yes X No
	AP3	WO 99/47154	09/23/1999	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	3	Braun, J.S. et al., "Neuroprotection by a caspase inhibitor in acute bacterial meningitis," Nat. Med. 5:298-302, Nature Publishing Group (March 1999).
	AS	3	Chabrier, P.-E. et al., "BN 80933, a dual inhibitor of neuronal nitric oxide synthase and lipid peroxidation: A promising neuroprotective strategy," Proc. Natl. Acad. Sci. USA 96:10824-10829, The National Academy of Sciences (September 1999).
	AT	3	Conaldi, P.G. et al., "HIV-1 Kills Renal Tubular Epithelial Cells In Vitro by Triggering an Apoptotic Pathway Involving Caspase Activation and Fas Upregulation," J. Clin. Invest. 102:2041-2049, The American Society for Clinical Investigation, Inc. (December 1998).

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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL4	WO 99/56765	11/11/1999	WIPO			Yes No
	AM4	WO 00/01666	01/13/2000	WIPO			Yes No
	AN4	WO 00/23421	04/27/2000	WIPO			Yes No
	AO4	WO 00/32620 A1	06/08/2000	WIPO			Yes No
	AP4	WO 00/55114 A1	09/21/2000	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>4</u>	del Pozo, O. and Lam, E., "Caspases and programmed cell death in the hypersensitive response of plants to pathogens," <i>Curr. Biol.</i> 8:1129-1132, Current Biology Ltd. (September 1998).
	AS	<u>4</u>	di Giovine, F.S. and Duff, G.W., "Interleukin 1: the first interleukin," <i>Immunol. Today</i> 11:13-14, Elsevier Science Publishers Ltd. (1990).
	AT	<u>4</u>	Dinarello, C. A., "Interleukin-1 and Interleukin-1 Antagonism," <i>Blood</i> 77:1627-1652, The American Society of Hematology (1991).

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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB- CLASS	TRANSLATION
	AL5	WO 00/55127 A1	09/21/2000	WIPO			Yes No
	AM5	WO 00/61542	10/19/2000	WIPO			Yes No
	AN5	WO 01/10383 A2	02/15/2001	WIPO			Yes No
	AO5	WO 01/42216 A2	06/14/2001	WIPO			Yes No
	AP5	WO 01/16093 A1	03/08/2001	WIPO			Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>5</u>	Dolle, R.E. et al., "P ₁ Aspartate-Based Peptide α -((2,6-Dichlorobenzoyl)oxy)methyl Ketones as Potent Time-Dependent Inhibitors of Interleukin-1 β -Converting Enzyme," <i>J. Med. Chem.</i> 37:563-564, American Chemical Society (1994).
	AS	<u>5</u>	Dolle, R.E. et al., "Aspartyl α -((1-Phenyl-3-(trifluoromethyl)-pyrazol-5-yl)oxy)methyl Ketones as Interleukin-1 β Converting Enzyme Inhibitors. Significance of the P ₁ and P ₂ Amido Nitrogens for Enzyme-Peptide Inhibitor Binding," <i>J. Med. Chem.</i> 37:3863-3866, American Chemical Society (1994).
	AT	<u>5</u>	Dolle, R.E. et al., "Aspartyl α -((Diphenylphosphinyl)oxy)methyl Ketones as Novel Inhibitors of Interleukin-1 β Converting Enzyme. Utility of the Diphenylphosphinic Acid Leaving Group for the Inhibition of Cysteine Proteases," <i>J. Med. Chem.</i> 38:220-222, American Chemical Society (1995).

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FOREIGN PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL6	WO 01/27140 A1	04/19/2001	WIPO			Yes No
	AM6	WO 01/72707 A2	10/04/2001	WIPO			Yes No
	AN6	WO 01/90070 A2	11/29/2001	WIPO			Yes No
	AO6	WO 01/94351 A1	12/13/2001	WIPO			Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>6</u>	Ellis, R.E. et al., "Mechanisms and Functions of Cell Death," Annu. Rev. Cell Biol. 7:663-698, Annual Reviews Inc. (1991).
	AS	<u>6</u>	Emery, E. et al., "Apoptosis after traumatic human spinal cord injury," J. Neurosurg. 89:911-920, American Association of Neurological Surgeons (December 1998).
	AT	<u>6</u>	Fukuzuka, K. et al., "Caspase-3-Dependent Organ Apoptosis Early After Burn Injury," Ann. Surg. 229:851-859, Lippincott Williams & Wilkins, Inc. (June 1999).

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	2	Goldberg, Y.P. et al., "Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract," <i>Nat. Genet.</i> 13:442-449, Nature Publishing Group (1996).
	AS	2	Graybill, T.L. et al., " α -((Tetronoyl)oxy)- and α -((Tetramoyl)oxy)methyl Ketone Inhibitors of the Interleukin-1 β Converting Enzyme (ICE)," <i>Bioorg. Med. Chem. Lett.</i> 7:41-46, Elsevier Science Ltd. (1997).
	AT	2	Greenberg, J.T. et al., "Programmed Cell Death in Plants: A Pathogen-Triggered Response Activated Coordinately with Multiple Defense Functions," <i>Cell</i> 77:551-563, Cell Press (1994).

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	AO						Yes No
	AP						Yes No

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	AR	8	Grobmyer, S.R. et al., "Peptidomimetic Fluoromethylketone Rescues Mice from Lethal Endotoxic Shock," <i>Mol. Med.</i> 5:585-594, The Picower Institute Press (September 1999).
	AS	8	Hara, H. et al., "Inhibition of interleukin 1 β converting enzyme family proteases reduces ischemic and exitotoxic neuronal damage," <i>Proc. Natl. Acad. Sci. USA</i> 94:2007-2012, The National Academy of Sciences (1997).
	AT	8	Hiraoka, J. et al., "Participation of apoptosis in renal amyloidosis," <i>Jpn. J. Nephrol.</i> 40:276-283, Japanese Society of Nephrology (May 1998).

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	2	Hotchkiss, R.S. et al., "Prevention of lymphocyte cell death in sepsis improves survival in mice," <i>Proc. Natl. Acad. Sci.</i> 96:14541-14546, The National Academy of Sciences (December 1999).
	AS	2	Jaeschke, H. et al., "Activation of Caspase 3 (CPP32)-Like Proteases Is Essential for TNF- α -Induced Hepatic Parenchymal Cell Apoptosis and Neutrophil-Mediated Necrosis in a Murine Endotoxin Shock Model," <i>J. Immun.</i> 160:3480-3486, The American Association of Immunologists (April 1998).
	AT	2	Jones, R.A. et al., "Fas-Mediated Apoptosis in Mouse Hepatocytes Involves the Processing and Activation of Caspases," <i>Hepatology</i> 27:1632-1642, The American Association for the Study of Liver Diseases (June 1998).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>10</u>	Kermer, P. et al., "Inhibition of CPP32-Like Proteases Rescues Axotomized Retinal Ganglion Cells from Secondary Cell Death <i>In Vivo</i> ," <i>J. Neuroscience</i> 18:4656-4662, Society for Neuroscience (June 1998).
	AS	<u>10</u>	Kubo, S. et al., "Hepatocyte injury in tyrosinemia type 1 is induced by fumarylacetoacetate and is inhibited by caspase inhibitors," <i>Proc. Natl. Acad. Sci. USA</i> 95:9552-9557, The National Academy of Sciences (August 1998).
	AT	<u>10</u>	Lepschy, J., "Acylierung von Oxazolinonen-(5) unter besonderer Berücksichtigung der Dakin-West-Reaktion trifunktioneller Aminosäuren," <i>Ph.D. Thesis</i> , Technischen Universität München (1971).

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	AR	<u>11</u>	Lieberthal, W. et al., "Necrosis and Apoptosis in Acute Renal Failure," <i>Sem. Nephrol.</i> 18:505-518, W.B. Saunders Company (September 1998).
	AS	<u>11</u>	Lotem, J. and Sachs, L., "Differential suppression by protease inhibitors and cytokines of apoptosis induced by wild-type p53 and cytotoxic agents," <i>Proc. Natl. Acad. Sci. USA</i> 93:12507-12512, The National Academy of Sciences (1996).
	AT	<u>11</u>	Mattson, M.P. et al., "Amyloid β -peptide induces apoptosis-related events in synapses and dendrites," <i>Brain Res.</i> 807:167-176, Elsevier Science B.V. (October 1998).

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	AP						Yes No

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	AR	<u>12</u>	Maulik, N. et al., "Oxidative stress developed during the reperfusion of ischemic myocardium induces apoptosis," <i>Free Rad. Biol. & Med.</i> 24:869-875, Eslsevier Science Inc. (March 1998).
	AS	<u>12</u>	Miller, P.E. et al., "Photoreceptor cell death by apoptosis in dogs with sudden acquired retinal degeneration syndrome," <i>Am. J. Vet. Res.</i> 59:149-152, American Veterinary Medical Association (February 1998).
	AT	<u>12</u>	Miura, M. et al., "Induction of Apoptosis in Fibroblasts by IL-1 β -Converting Enzyme, a Mammalian Homolog of the C. elegans Cell Death Gene ced-3," <i>Cell</i> 75:653-660, Cell Press (1993).

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	AR	<u>13</u>	Mjalli, A.M.M. et al., "Phenylalkyl Ketones as Potent Reversible Inhibitors of Interleukin-1 β Converting Enzyme," <i>Bioorg. Med. Chem. Lett.</i> 3:2689-2692, Pergamon Press Ltd. (1993).
	AS	<u>13</u>	Mjalli, A.M.M. et al., "Activated Ketones as Potent Reversible Inhibitors of Interleukin-1 β Converting Enzyme," <i>Bioorg. Med. Chem. Lett.</i> 4:1965-1968, Elsevier Science Ltd. (1994).
	AT	<u>13</u>	Mjalli, A.M.M. et al., "Inhibition of Interleukin-1 β Converting Enzyme by N-Acyl-Aspartic Acid Ketones," <i>Bioorg. Med. Chem. Lett.</i> 5:1405-1408, Elsevier Science Ltd. (1995).

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	AR	<u>14</u>	Mjalli, A.M.M. et al., "Inhibition of Interleukin-1 β Converting Enzyme by N-Acyl-Aspartyl Aryloxymethyl Ketones," <i>Bioorg. Med. Chem. Lett.</i> 5:1409-1414, Elsevier Science Ltd. (1995).
	AS	<u>14</u>	Morrison, R.T. and Boyd, R.N., "Structure and Properties. Alkyl Halides," in <i>Organic Chemistry</i> , Morrison, R.T. and Boyd, R.N., Eds., Allyn and Bacon, Inc., Boston, MA, pp. 22 and 456 (1973).
	AT	<u>14</u>	Mosley, B. et al., "The Interleukin-1 Receptor Binds the Human Interleukin-1 α Precursor but Not the Interleukin-1 β Precursor," <i>J. Biol. Chem.</i> 262:2941-2944, The American Society of Biological Chemists, Inc. (1987).

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	AR	<u>15</u>	Mundle, S. D. et al., "Evidence for Involvement of Tumor Necrosis Factor- α in Apoptotic Death of Bone Marrow Cells in Myelodysplastic Syndromes," <i>Am. J. Hemat.</i> 60:36-47, Wiley-Liss, Inc. (January 1999).
	AS	<u>15</u>	Okamoto, Y. et al., "Peptide Based Interleukin-1 β Converting Enzyme (ICE) Inhibitors: Synthesis, Structure Activity Relationships and Crystallographic Study of the ICE-Inhibitor Complex," <i>Chem. Pharm. Bull.</i> 47:11-21, Pharmaceutical Society of Japan (January 1999).
	AT	<u>15</u>	Oppenheim, J.J., et al., "There is more than one interleukin 1," <i>Immun. Today</i> 7:45-56, Elsevier Science Publishers B.V. (1986).

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	AP						Yes No

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	AR	<u>16</u>	Orrenius, S., "Apoptosis: molecular mechanisms and implications for human disease," <i>J. Internal Med.</i> 237:529-536, Blackwell Science Ltd. (1995).
	AS	<u>16</u>	Ortiz, A. et al., "Cyclosporine A induces apoptosis in murine tubular epithelial cells: Role of caspases," <i>Kidney Int'l</i> 54:S-25-S-29, International Society of Nephrology (December 1998).
	AT	<u>16</u>	Rasnick, D., "Synthesis of Peptide Fluoromethyl Ketones and the Inhibition of Human Cathepsin B," <i>Anal. Biochem.</i> 149:461-465, Academic Press, Inc. (1985).

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	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>17</u>	Rauber, P. et al., "The synthesis of peptidylfluoromethanes and their properties as inhibitors of serine proteinases and cysteine proteinases," <i>Biochem. J.</i> 239:633-640, The Biochemical Society (1986).
	AS	<u>17</u>	Revesz, L. et al., "Synthesis of P1 Aspartate-Based Peptide Acyloxymethyl and Fluoromethyl Ketones as Inhibitors of Interleukin-1 β -Converting Enzyme," <i>Tet. Lett.</i> 35:9693-9696, Elsevier Science Ltd. (1994).
	AT	<u>17</u>	Rich, D.H., "Inhibitors of aspartic proteinases," in <i>Proteinase inhibitors. Research monographs in cell and tissue physiology.</i> Volume 12, Barrett, A.J. and G. Salvesen, eds., Elsevier, Amsterdam, Holland, pp.179-208 (1986).

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OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>18</u>	Richberg, M.H. et al., "Dead cells do tell tales," Curr. Opin. Plant Biol. 1:480-485, Current Biology Ltd. (December 1998).
	AS	<u>18</u>	Rodriguez, I. et al., "Systemic Injection of a Tripeptide Inhibits the Intracellular Activation of CPP32-like Proteases In Vivo and Fully Protects Mice against Fas-mediated Fulminant Liver Destruction and Death," J. Exp. Med. 184:2067-2072, The Rockefeller University Press (1996).
	AT	<u>18</u>	Schierle, G.S. et al., "Caspase inhibition reduces apoptosis and increases survival of nigral transplants," Nat. Med. 5:97-100, Nature Publishing Group (January 1999).

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	AR	19	Semple, G. et al., "Peptidomimetic Aminomethylene Ketone Inhibitors of Interleukin-1 β -Converting Enzyme (ICE)," <i>Bioorg. Med. Chem. Lett.</i> 8:959-964, Elsevier Science Ltd. (April 1998).
	AS	19	Shaw, E. et al., "Peptidyl fluoromethyl ketones as thiol protease inhibitors," <i>Biomed. Biochim. Acta</i> 45:1397-1403, Akademie Verlag (1986).
	AT	19	Sheikh, M.S. et al., "Ultraviolet-irradiation-induced apoptosis is mediated via ligand independent activation of tumor necrosis factor receptor 1," <i>Oncogene</i> 17:2555-2563, Stockton Press (November 1998).

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	AS	<u>20</u>	Slomiany, B.L. et al., "Activation of Apoptotic Caspase-3 and Nitric Oxide Synthase-2 in Buccal Mucosa with Chronic Alcohol Ingestion," <i>Biochem. Mol. Biol. Int'l.</i> 45:1199-1209, Academic Press Australia (September 1998).
	AT	<u>20</u>	Springer, J.E. et al., "Activation of the caspase-3 apoptotic cascade in traumatic spinal cord injury," <i>Nat. Med.</i> 5:943-946, Nature America Incorporated (August 1999).

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	AR	<u>21</u>	Steinberg, D., "Caspase Inhibitors. Molecules Sought For Treatment of Diverse Disorders," <i>Gen. Eng. News</i> 18:16,38,51, Mary Ann Leibert, Inc. (July 1998).
	AS	<u>21</u>	Suzuki, A., "The Dominant Role of CPP32 Subfamily in Fas-Mediated Hepatitis," <i>Proc. Soc. Exp. Biol. Med.</i> 217:450-454, The Society for Experimental Biology and Medicine (April 1998).
	AT	<u>21</u>	Thornberry, N.A. et al., "A novel heterodimeric cysteine protease is required for interleukin-1 β processing in monocytes," <i>Nature</i> 356:768-774, Nature Publishing Group (1992).

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	AR	<u>22</u>	Thornberry, N.A. et al., "Inactivation of Interleukin-1 β Converting Enzyme by Peptide (Acyloxy)methyl Ketones," <i>Biochemistry</i> 33:3934-3940, American Chemical Society (1994).
	AS	<u>22</u>	Thornberry, N.A. et al., "A Combinatorial Approach Defines Specificities of Members of the Caspase Family and Granzyme B," <i>J. Biol. Chem.</i> 272:17907-17911, The American Society for Biochemistry and Molecular Biology, Inc. (1997).
	AT	<u>22</u>	Thornberry, N.A., "Caspases: key mediators of apoptosis," <i>Chem. & Biol.</i> 5:R97-R103, Current Biology Ltd. (May 1998).

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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>23</u>	Wataya, Y. et al., "Cytotoxic mechanism of 1-(3-C-ethynyl-β-D-ribo-pentofuranosyl)cytosine (Ecyd)," <i>Chemical Abstracts</i> 132:273983, Abstract No. 273983p, The American Chemical Society (May 2000).
	AS	<u>23</u>	Weil, M. et al., "Is programmed cell death required for neural tube closure?" <i>Curr. Biol.</i> 7:281-284, Current Biology Ltd. (1997).
	AT	<u>23</u>	Wyllie, A.H. et al., "Cell Death: The Significance of Apoptosis," <i>Int. Rev. Cytol.</i> 68:251-306, Academic Press, Inc. (1980).

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.	

FORM PTO-1449 <u>INFORMATION DISCLOSURE STATEMENT</u>				ATTY. DOCKET NO. 1735.0350004/RWE/BLS		APPLICATION NO. 10/721,338	
				APPLICANTS Cai et al.			
				FILING DATE November 26, 2003		GROUP To Be Assigned	

U.S. PATENT DOCUMENTS							
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	AL						Yes No
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	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>24</u>	Wyllie, A.H., "Cell death: a new classification separating apoptosis from necrosis," in <i>Cell Death in Biology and Pathology</i> , Bowen, I.D. and R.A. Lockshin, eds., Chapman and Hall, New York, NY, pp. 9-34 (1981).
	AS	<u>24</u>	Xue, D. et al., "The Time Course for Infarction in a Rat Model of Transit Focal Ischemia," <i>Stroke</i> 21:166, Abstract No. 36, American Heart Association (1990).
	AT	<u>24</u>	Yuan, J. et al., "The C. elegans Cell Death Gene ced-3 Encodes a Protein Similar to Mammalian Interleukin-1 β -Converting Enzyme," <i>Cell</i> 75:641-652, Cell Press (1993).

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	AM						Yes No
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	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)			
	AR	<u>25</u>	International Search Report for International Application No. PCT/US00/09319, mailed August 14, 2000.
	AS	<u>25</u>	Dialog File 351, Accession No. 12319369, Derwent WPI English language abstract for JP 11-1491 (Document AM3).
	AT	<u>25</u>	WPINDEX, Accession No. 1999-439401, Derwent WPI English language abstract for JP 11-180891 (Document AO3).

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	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	<u>26</u>	Copy of European Search Report for European Application No. 00921874, mailed May 13, 2003, European Patent Office, Netherlands
	AS	<u>26</u>	U.S. Application No. 10/429,095, filed May 5, 2003 (pending), Keana, et al.
	AT	<u>26</u>	U.S. Application No. 10/434,335, filed May 9, 2003 (pending), Cai, et al.

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